

SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Name: Contraceptive Tubal Occlusion Device and
Delivery System

Device Trade Name: Essure? Permanent Birth Control System

**Applicant's Name and
Address:** Conceptus, Incorporated
1021 Howard Avenue
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Premarket Approval Application (PMA) Number: P020014

Date of Panel Recommendation: To be provided by FDA

Date of Notice of Approval to Applicant: To be provided by FDA

II. INDICATION FOR USE

The Essure? System is indicated for permanent birth control (female sterilization) by occlusion of the fallopian tubes.

III. DEVICE DESCRIPTION

The **Essure Permanent Birth Control System** is designed to provide a non-incisional alternative to women seeking permanent contraception. Using a transcervical approach, one **Essure** Micro-insert is placed in the proximal section of each fallopian tube lumen. When the **Essure** Micro-insert expands upon release, it acutely anchors itself in the fallopian tube. Subsequently, the **Essure** Micro-insert elicits an intended benign occlusive tissue response, resulting in

tissue in-growth into the device that permanently anchors the device and occludes the fallopian tube, resulting in permanent contraception.

The **Essure Permanent Birth Control System** is comprised of the following:

- ? the **Essure** Micro-insert
- ? a disposable delivery system, and
- ? a disposable Split Introducer.

The **Essure** Micro-insert is a dynamically expanding Micro-coil that consists of a stainless steel inner coil, a Nickel Titanium (nitinol) expanding, superelastic outer coil, and polyethylene (PET) fibers. The PET fibers are wound in and around the inner coil. The Micro-insert, shown in **Figure 1** below, is 4 cm in length and 0.8mm in diameter in its wound down configuration. When released from the delivery system, the outer coil expands to 1.5 to 2.0 mm in diameter to anchor the Micro-insert in the varied diameters and shapes of the fallopian tube.

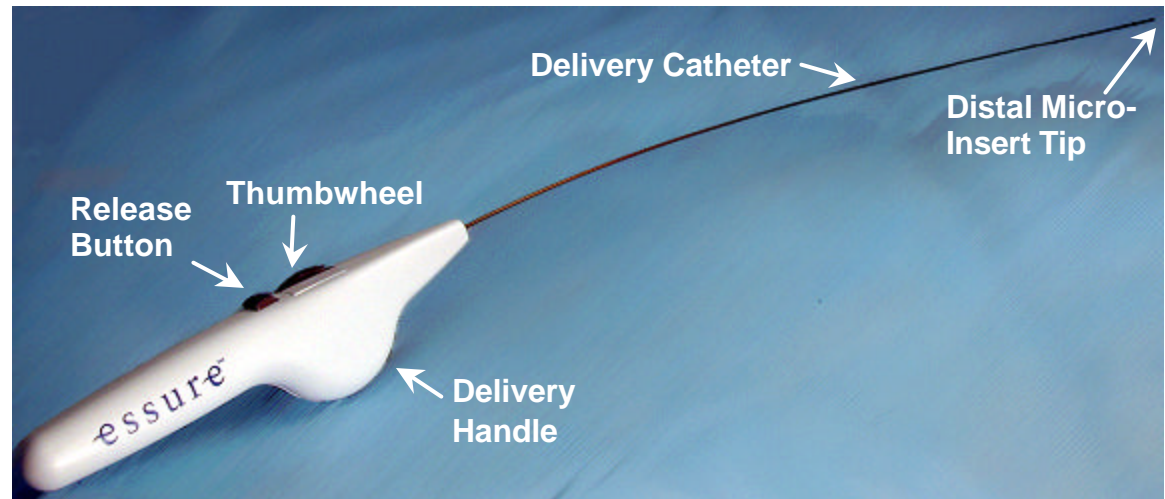
Figure 1
Essure Micro-insert (Shown in its Expanded Configuration)

Wound Down Diameter 0.8 mm
Expanded Diameter 1.5 – 2.0 mm



The disposable delivery system, shown is **Figure 2** below, consists of a delivery wire, a release catheter, a delivery catheter and a delivery handle.

Figure 2
Essure Delivery System



NOTE: The delivery wire and the release catheter are not visible in the figure shown above.

The **Essure** Micro-insert is provided attached to the delivery wire, in a wound-down (low profile) configuration. The delivery wire is composed of a nitinol core wire, which is ground at the distal end to result in a flexible, tapered profile. The device is constrained by the release catheter which is sheathed by a flexible delivery catheter. A positioning bump on the tubing aids in proper placement of the device in the fallopian tube.

The delivery handle controls the device delivery and release mechanism. The thumbwheel on the delivery handle retracts both the delivery catheter and the release catheter. The button allows the physician to change the function of the thumbwheel from retracting the delivery catheter to retracting the release catheter. The delivery wire is detached from the Micro-insert by rotating the system.

The Split Introducer is intended to help protect the **Essure** Micro-insert as it is being passed through the rubber port of the hysteroscope working channel.

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

CONTRAINDICATIONS

The **Essure Permanent Birth Control System** should not be used in any patient who is:

- ? Uncertain about her desire to end fertility.
- ? Currently taking systemic corticosteroids.

Or any patient with any of the following conditions:

- ? Pregnancy or suspected pregnancy.
- ? Delivery or termination of a second trimester pregnancy less than 6 weeks before **Essure** Micro-insert placement.
- ? Active or recent pelvic infection.
- ? Untreated acute cervicitis.
- ? Gynecological malignancy (suspected or known).
- ? Known abnormal uterine cavity or fallopian tubes that would make visualization of the tubal ostia and/or cannulation of the proximal fallopian tube difficult or impossible.
- ? Known allergy to contrast media.
- ? Known hypersensitivity to nickel confirmed by skin test.

WARNINGS

- ? Whenever possible, Micro-insert placement should be performed during days 7-14 of the menstrual cycle (where day 1 represents the first day of bleeding) in order to decrease the potential for Micro-insert placement in a patient with an undiagnosed (luteal phase) pregnancy and enhance visualization of the fallopian tube ostia.

- ? When introducing the **Essure** Micro-insert into the fallopian tube, never advance the Micro-insert(s) against excessive resistance.
- ? In order to reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.
- ? If tubal or uterine perforation occurs or is suspected, immediately discontinue the **Essure** placement procedure.
- ? Do not continue to advance the **Essure** System once the positioning bump on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory Micro-insert placement and/or tubal/uterine perforation.
- ? Once the Micro-insert has been placed, Micro-insert removal should not be attempted hysteroscopically, unless 18 or more coils of the **Essure** Micro-insert are trailing into the uterine cavity. Removal of such a Micro-insert should be attempted immediately following the placement; however, removal may not be possible.
- ? The patient cannot rely on the **Essure** Micro-inserts for contraception and must use alternative contraception until an x-ray performed three months post-Micro-insert placement demonstrates satisfactory Micro-insert location.
- ? Following placement of the **Essure** Micro-inserts, it is recommended that electrocautery be avoided in surgical procedures undertaken on the uterine cornua and fallopian tubes. In other procedures in the pelvis, avoid the use of electrocautery within 4 cm of the Micro-insert. Due to the presence of the **Essure** Micro-inserts, there may be risks associated with such procedures that, at this time, have not been identified.
- ? Any intrauterine procedure such as endometrial biopsy, D&C, hysteroscopy (diagnostic or operative) including endometrial ablation, could interrupt the ability of the Micro-inserts to prevent pregnancy. In addition, the presence of the **Essure** Micro-inserts could entail risks associated with such procedures that, at this time, have not been identified.
- ? There are no data on the safety or effectiveness of surgery to reverse the **Essure** procedure.

- ? Patients may decide, in future years, to undergo *in vitro* fertilization (IVF) to become pregnant. The effects of the **Essure** Micro-inserts on the success of IVF are unknown. If pregnancy is achieved, the risks of the Micro-insert to the patient, to the fetus and to the continuation of a pregnancy are also unknown.
- ? Do not use the **Essure** System if the sterile package is open or damaged. Do not use if the Micro-insert is damaged.

PRECAUTIONS

- ? Testing to ensure safety and compatibility with Magnetic Resonance Imaging (MRI) has been conducted using a 1.5 Tesla magnet. The **Essure** Micro-inserts were found to be MR safe at this field strength. However, the presence of the Micro-inserts produces an MR artifact which will obscure imaging of local tissue.
- ? Unusual uterine anatomy may make it difficult to place the **Essure** Micro-inserts.
- ? If **Essure** Micro-insert placement attempts are not successful after 10 minutes of attempted cannulation per tube, the case should be terminated and potentially rescheduled.
- ? Both tubal ostia should be identified and assessed hysteroscopically prior to proceeding to **Essure** Micro-insert placement. No attempt should be made to place a Micro-insert in one tubal ostium unless there is a reasonable expectation that the opposite tube is accessible and patent.
- ? Do not advance the **Essure** System if the patient is experiencing extraordinary pain or discomfort.
- ? For single use only. Never attempt to resterilize an **Essure** Micro-insert or delivery system.
- ? When removing the metal obturator from the introducer, there is a possibility that saline will be washed back through the operating channel of the hysteroscope. Proper eye and face protection should be utilized.

V. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A. Patient Population

A total of 677 women (implanted with a total of 1,341 devices) who participated in two separate clinical investigations to evaluate the safety and effectiveness of the **Essure Permanent Birth Control System** provides the basis of the observed adverse event rates presented in this section. The total device exposure for this patient population is equivalent to over 1000 patient years.

B. Patient Deaths

A total of no (0) patient deaths were reported in this patient population.

C. Observed Adverse Events

The following adverse events were reported with the Essure Micro-insert: expulsion (2.2%), perforation (1.5%), other unsatisfactory device location (0.6%).

Other adverse events or side effects reported as a result of the hysteroscopic placement procedure included:

Cramping (20%), nausea and vomiting (8%), dizziness or lightheadedness (5%), vasovagal response (1%), hypervolemia (0.2.%), and proximal band detachment (0.6%). In addition, the majority of women experienced mild to moderate pain during and immediately following the procedure, and the majority of women experienced spotting for an average of 3 days.

Table 1 summarizes all adverse events rated by the Investigators to be at least "possibly" related to the Micro-insert or Micro-insert placement procedure during the first year of reliance on Essure in the Pivotal trial

(approximately 15 months post-device placement and during the first 12 months post-device placement in the Phase II trial.

Table 1
Adverse Events by Body Systems, First Year *
(N=677 patients implanted with at least one device)

Adverse Events by Body System	Number	Percent
Abdominal:		
Abdominal pain/abdominal cramps	16	3.4%
Gas/bloating	6	1.3%
Musculo-skeletal:		
Back Pain/low Back Pain	40	8.4%
Arm/leg Pain	4	0.8%
Nervous/Psychiatric:		
Headache	12	2.5%
Premenstrual Syndrome	3	0.6%
Genitourinary:		
Dysmenorrhea/menstrual cramps (severe)	11	2.3%
Pelvic/lower abdominal pain (severe)	12	2.5%
Persistent increase in menstrual flow		1.9%
Vaginal discharge/vaginal infection	9**	1.5%
Abnormal bleeding - timing not specified (severe)	7	1.1%
Menorrhagia/prolonged menses (severe)	5	1.1%
Dyspareunia	5	2.9
	14	
Pain/discomfort - uncharacterized:	14	2.9%

* Only events occurring in ? 0.5% are reported

** Eight women reported persistent *decrease* in menstrual flow.

D. Potential Adverse Events Not Observed in Clinical Studies

The following adverse events were not experienced by women who participated in clinical studies evaluating the **Essure Permanent Birth Control System** but are still possible:

- ? Pregnancy and ectopic pregnancy in women relying on Essure¹
- ? Perforation (a small hole) in internal bodily structures other than the uterus and fallopian tube.
- ?? Risk of adnexal infection/salpingitis.
- ? Risks associated with the hysterosalpingogram or X-rays.
- ? The effect of future medical procedures that involve the uterus or fallopian tubes on the ability of the **Essure** Micro-insert to provide protection against pregnancy.
- ? Risks associated with surgery to reverse the **Essure** procedure.

There is the potential that unknown risks exist.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative permanent female methods of sterilization include hysterectomy, salpingectomy, ligation, fulguration, and application of clips. The permanent male method is vasectomy. There are also numerous forms of temporary, reversible methods.

VII. MARKETING HISTORY

The Essure System is currently commercially available in the following countries: Australia, certain European countries, Singapore, and Canada. Registration of the product for commercial sale in Australia and Singapore was completed with the appropriate regulatory authorities. CE Mark approval was granted by TUV in February, 2001, and a Medical Device License was granted by Health Canada in November, 2001.

VIII. SUMMARY OF STUDIES

¹ One woman in the Phase II study who received a prior device design that was discontinued in 1998 (the Beta design of the STOP device) became pregnant after nearly two years of reliance. That pregnancy is not included in the effectiveness rate calculations, since that device design is not the subject of this PMA.

A. Pre-clinical studies

1. Concept Testing of the Essure System

Concept testing was performed in the initial design evaluation. The objective of the concept testing was to help design the Essure System for optimal safety and performance. The concept testing consisted of: Evaluation of navigation and deployment in pig fallopian tubes and varying fixtures; Tensile testing of raw materials, solder bonds and subassemblies; Initial tip fatigue evaluation; Release mechanism testing; Delivery wire release testing; Handle process evaluation; Torque evaluation; Initial corrosion analysis; and, fibering evaluation.

2. Feasibility Testing of the Essure System

After concept testing, feasibility testing was performed to evaluate the ability of the design, process and test methods to produce a consistent product that meets the design input specifications. The feasibility testing included the following: positioning marker evaluation; catheter tip integrity testing; fiber configuration testing; tracking and retraction evaluation in multiple orientations; tensile testing of subassemblies; handle functional testing; nitinol flux evaluation, and corrosion/leaching evaluation. Feasibility testing was also conducted in Peri-hysterectomy patients (see clinical studies section below).

3. Verification Testing of the Essure System

Verification activities included worst-case (tolerance) analysis, FMEA review, packaging integrity, clinical testing, biocompatibility, bioburden, as well as comparisons to previous designs/products using multiple methods such as testing, inspection, and technical analysis. The design and process

verification testing for the Essure System consists of: tensile testing to show design and process repeatability; functional testing; environmental cycle testing of the finished Essure System to show material and component stability; tracking force testing; flexibility testing; anchoring testing; raw material specification verification; chemical analysis of the etched nitinol material; corrosion analysis of the Essure Micro-insert; and MRI testing.

2. Biocompatibility

The Essure System has undergone extensive biocompatibility testing; the following studies have been performed:

Body Contact		Contact Duration	Biologic Tests Conducted
Delivery System	Surface Device with Tissue Contact	A– Limited (<24 hrs)	1. Cytotoxicity 2. Sensitization 3. Irritation
Micro-insert	Implant Device with Tissue Contact	C– Permanent (>30 days)	1. Cytotoxicity 2. Sensitization 3. Genotoxicity 4. Implantation 5. Irritation 6. <i>In Vivo</i> Mutagenicity 7. Sub Chronic Toxicity 8. Acute Systemic Toxicity

Extracts prepared from the Micro-insert did not exhibit any detectable toxicity during biocompatibility testing. Muscle implantation studies of the Micro-insert in rabbits demonstrated an inflammatory response consistent with the desired *in vivo* reactions to polyethylene terephthalate (PET) fiber described in the medical literature and with the theorized mechanism of action of the Essure Micro-insert. A multitude of medical devices that rely on this inflammatory response to stimulate tissue in-growth have

successfully utilized this material in their construction for over 40 years.

Polar and non-polar extracts of the Essure Micro-insert did not elicit any evidence of *in vitro* cytotoxicity or *in vivo* delayed dermal contact sensitization. Similarly, extracts of the Essure Micro-insert did not elicit vaginal irritation or any evidence of acute or sub-chronic systemic toxicity. In addition, evaluations of genotoxicity (bacterial reverse mutation, mouse lymphoma, mouse bone marrow micronucleus test and chromosomal aberrations tests) did not reveal any mutagenic or genotoxic effect of the Essure Micro-insert. Implantation of either one or three Essure Micro-inserts into C57B16 *lasI/cII p53^{+/-}* transgenic mice resulted in no adverse toxicological effects and no increase in gene mutations at the site of implantation. Lastly, the implantation of the Essure Micro-insert in the paravertebral muscle of rabbits over a 26-week implantation period demonstrated that the Essure Micro-insert was not systemically or locally toxic.

Extensive biocompatibility testing of the Essure Micro-insert and Delivery System has been conducted and the data supports the biocompatibility of the entire system. In addition, the data obtained from the biocompatibility testing of Essure are consistent with the long history of safe use of the biomaterials contained in the Essure Micro-insert as well as the well-characterized *in vivo* response to the PET fiber.

3. Animal Studies

Three separate animal studies were performed during the initial stages of development of the Essure Micro-insert. These studies evaluated earlier device designs and were intended to provide early

proof of concept and effectiveness data. The studies supported the feasibility of the device concept.

5. Shelf-Life Testing

Conceptus has conducted shelf life studies to establish and support expiration dating for the Essure System. These studies include an Environmental Conditioning and Package Performance (Shipping) study, a Real Time Aging study, and an Accelerated Aging study to establish a 24-month shelf life. The Shipping study and the Accelerated Aging study have been completed and the Real Time aging study is in progress. To date the shelf-life has been validated for 2-years, based on accelerated aging studies.

B. Summary of Clinical Studies

1. Description of Clinical Studies

The PMA included data from 4 clinical studies: a Peri-hysterectomy study, a Pre-hysterectomy study, a Phase II study of safety and effectiveness, and a Pivotal Trial of safety and effectiveness. More detail is provided on each study in Section C. A total of 907 women underwent the Essure procedure in the 4 trials, and 643 women have been followed up for safety and effectiveness in the Phase II and Pivotal Trials (an additional five women have been followed who are relying on only a single device). Further detail is given below for the Phase II and the Pivotal trial.

a. Purpose of the Study, Study Design, Primary Endpoints

The purpose of both studies was to evaluate the safety and effectiveness of the **Essure Permanent Birth Control System** in providing permanent contraception.

The Phase II study was a prospective, multi-center, international study of women seeking permanent contraception. The objectives of the study were to evaluate:

- ? The woman's tolerance of, and recovery from, the Micro-insert placement procedure;
- ? The safety of the Micro-insert placement procedure;
- ? The woman's tolerance of the implanted Micro-inserts;
- ? The long-term safety and stability of the implanted Micro-inserts; and
- ? The effectiveness of the Micro-inserts in preventing pregnancy.

The Pivotal study was a prospective, multi-center international study of women seeking permanent contraception. The study used findings from the U.S. Collaborative Review of Sterilization (CREST¹ study) as a qualitative benchmark. The primary endpoints for the study included:

- ? Prevention of pregnancy;
- ? Safety of device placement procedure, and;
- ? Safety of device wearing.

The secondary endpoints for the study included:

- ? Participant satisfaction with device placement procedure;
- ? Participant satisfaction with device wearing;
- ? Bilateral device placement rate, and;

- ? Development of a profile for an appropriate candidate for the Essure procedure.

b. Patients Studied

The study population of the two studies combined consisted of 664 women in whom bilateral device placement was achieved. All study participants were between 21 and 45 years of age and were seeking permanent contraception prior to enrollment in the study. Additionally, all women had at least one live birth, had regular, cyclical menses and were able and willing to use alternative contraception for the first three months following **Essure** device placement.

c. Methods

All study participants were screened for eligibility to participate in the clinical study. A complete medical history was obtained. A physical examination, a pelvic examination and required laboratory tests (including a pregnancy test) were conducted.

An **Essure** device placement procedure was attempted on each fallopian tube. In the Pivotal Trial, a pelvic x-ray was performed within 24 hours following device placement to serve as a baseline evaluation of device location.

Participants were instructed to use either a barrier contraceptive method or oral contraceptives for the first 3 months following the device placement procedure.

A hysterosalpingogram (HSG) was performed three months post device placement to evaluate device location and fallopian tube occlusion. If both fallopian tubes were

occluded and both devices were satisfactorily placed within the fallopian tubes, the participant was instructed to discontinue use of alternative contraception and use only the **Essure** devices for prevention of pregnancy.

d. Results

Of the 643 women enrolled in the clinical trials (with bilateral Micro-insert placement) and who relied on the **Essure Permanent Birth Control System** for contraception, no (0) pregnancies were reported²³. Adverse events that were reported in the clinical study are summarized in **Section V. C.** above, and events by study are provided below.

Table 2 presents the principal safety and effectiveness results.

Table 2
Principal Safety and Effectiveness Results

Outcome	Phase II N=227		Pivotal N=507	
	Number	Percent	Number	Percent
Bilateral Placement	200/227	88%	464/507	92%
Reliance Rate (among bilateral placements)	194/200	97%	449/464	97%
One-year Effectiveness Rate	-	99.5%	-	99.8%
Two-year Effectiveness Rate	-	99.4%	-	-

² One woman in the Phase II study who received a prior device design that was discontinued in 1998 (the Beta design of the STOP device) became pregnant after nearly two years of reliance. That pregnancy is not included in the effectiveness rate calculations, since that device design is not the subject of this PMA.

³ There were 4 luteal phase pregnancies reported in the Pivotal trial (pregnancies occurring prior to Essure Micro-insert placement but not detected on the day of placement). None of these 4 women became pregnant while relying on Essure for contraception. Each of the pregnancies in these four women was terminated, and each of the four women was subsequently able to rely on Essure for contraception and has not reported a pregnancy while relying on Essure.

2. Effectiveness- Pregnancy Rates

Of the 643 women followed for effectiveness, there have been no reported pregnancies.

Follow-up from time of reliance ranges from 1-3 years in the Phase II study, and from 7-20 months in the Pivotal Trial. Both clinical trials utilized a Bayesian approach to calculate effectiveness rates. The 1-year effectiveness rate for the Phase II study was 99.5% (98.1-100%) and the second year estimated effectiveness was 99.4% (98.0-100%). The 1-year estimated effectiveness rate for the Pivotal Trial was 99.8% (99.2-100%). Utilizing data from the Phase II as a Bayesian prior, the estimated overall one-year effectiveness rate is 99.8% (99.4-100%).

3. Safety

See **Section V** above and **Section C** below.

C. Details of Clinical Studies

1. Peri-hysterectomy study

The specific objectives of the study were to:

- ?? Evaluate new Micro-insert placement techniques and delivery systems;
- ?? Assess acute tubal occlusion immediately after Micro-insert placement;

The study was a single arm, prospective, non-randomized, non-controlled, multi-center, international study to test the placement feasibility of various Micro-insert designs and design iterations.

Variables evaluated were: ability to cannulate the fallopian tube, ability to release the Micro-insert, ability to remove the guidewire catheter system, acute tubal occlusion, and acute retention of the Micro-insert (evaluated by the tug test).

The patient population consisted of women who were scheduled to undergo a hysterectomy, who met the inclusion and exclusion criteria, and who were willing to prolong the operative time of their hysterectomy procedure in order to have Micro-inserts placed while under anesthesia (general or regional).

The study demonstrated the feasibility of the Micro-insert to be reliably and safely placed in the fallopian tube at a reasonably high rate for this challenging patient population. The system was shown to be able to access 80% of tubes bilaterally and 6% unilaterally, despite preexisting uterine pathology. A Micro-insert could be placed bilaterally in 73% of participants and unilaterally in 13% of participants. Overall, a Micro-insert could be placed in 96% of the tubes accessed. The Micro-insert also showed its ability to acutely anchor in the fallopian tube in 95% of Micro-inserts tested. The placement procedure and Micro-insert were shown to be safe with only three adverse events (3%) reported, none of which had clinical sequelae. Immediate occlusion of the fallopian tube was demonstrated in 82% of tubes tested.

2. Prehysterectomy study

The objectives of the Pre-hysterectomy study were to evaluate:

?? Placement of the Micro-insert in the proximal portion of the fallopian tube, ideally so that the outer coil spans the uterotubal junction (UTJ);

- ?? Detachment of the Micro-insert from the delivery wire;
- ?? The woman's tolerance of and recovery from the Micro-insert placement procedure;
- ?? Micro-insert stability within the fallopian tube until the hysterectomy;
- ?? Occlusion of the fallopian tube within 24 hours to 12 weeks of Micro-insert placement,
- ?? The local tissue response to the Micro-insert; and,
- ?? The effect of fiber on the ability of the Micro-insert to create a local tissue response.

Participants were women with benign conditions scheduled for hysterectomy and who were willing to undergo Essure Micro-insert placement and wear the Micro-inserts from 24 hours to 12 weeks prior to hysterectomy.

Women were implanted with the Essure Micro-inserts. They were followed from 24 hours to 12 weeks, to the time of their hysterectomy. Within 72 hours prior to the hysterectomy, they underwent an HSG to determine tubal occlusion. At the time of hysterectomy, the uterus was x-rayed and Micro-insert location evaluated, the uterus was bivalved and examined for gross pathologic findings, and the tubes were removed and histologically evaluated. During the time of Micro-insert wearing, women recorded any side effects they experienced on a daily log.

The procedure was found to be safe with minimal post-procedure discomfort and sequelae and minimal adverse events. The short-term wearing of the Micro-insert, from one to 30 weeks was also found to be acceptable, with no side effects reported in the participant diaries.

While 3 perforations were noted at the time of hysterectomy, 2 were with the since discontinued Support Catheter. Women who experienced the perforations reported no discomfort or difference in tolerance to the Micro-inserts than women without perforation.

The local, occlusive, benign tissue response demonstrated by histological evaluation of the specimens supports the theorized mechanism of action. The acute inflammatory response and low level chronic inflammatory response is consistent with other devices that have used PET fibers. The reaction is confined, however, to the area immediately adjacent to the Micro-insert and does not extend beyond the tubal wall. Also, immediately distal to the Micro-insert, the tube resumes its normal appearance.

Based on the histological observations from this study, it is apparent that the response to the Essure Micro-insert is occlusive in nature and should provide for long-term Micro-insert retention as well as pregnancy prevention. This study demonstrated that the tissue in-growth reaction is predictable, occurred in all fibered specimens collected, was localized to the Micro-insert, and did not result in adverse clinical sequelae.

3. Phase II Study of Safety and Effectiveness

The objectives of this study were to evaluate:

- ?? The woman's tolerance of, and recovery from, the Micro-insert placement procedure;
- ?? The safety of the Micro-insert placement procedure;
- ?? The woman's tolerance of the implanted Micro-inserts;

- ?? The long-term safety and stability of the implanted Micro-inserts; and
- ?? The effectiveness of the Micro-inserts in preventing pregnancy.

This study was a prospective, multi-center, international study of women seeking permanent contraception. Investigational sites were located in the United States, Belgium, Spain, and Australia.

Study participants were women who were seeking permanent contraception.

All women filled out a questionnaire one week after Micro-insert placement, documenting any bleeding, discomfort or other symptoms they experienced following the procedure. They were also asked about their perceptions of the placement procedure. Women then kept diaries for 6 months detailing menstrual and sexual activity, as well as accompanying symptoms.

During the first three months following Micro-insert placement, women were required to use an alternative form of contraception. This alternative contraception period was to allow adequate time for the tissue in-growth process to occlude the fallopian tube. Women could choose a barrier method or oral contraceptives for their alternative contraception.

At three months post-procedure, women underwent a hysterosalpingogram (HSG) and an ultrasound (USG) or an HSG alone to determine Micro-insert position and retention, and to evaluate occlusion of the fallopian tubes. If the Micro-inserts were in a satisfactory location, women were advised to discontinue alternative contraception and rely on the Micro-inserts for contraception. Women were then followed at the 6, 12, and 18-

month post-procedure time points, and 24 months after discontinuation of alternative contraception.

The Essure Micro-insert placement procedure was found to be safe and acceptable to women. The procedure-related adverse events were within an expected and acceptable range for a hysteroscopic procedure, with less than 1% of women experiencing an adverse event on the day of the procedure. Adverse events experienced after the day of the procedure occurred in less than 4% of women.

The primary adverse event experienced was perforation (2.6%). Of the perforations, 4/6 (67%) utilized the Support Catheter that was associated with a high rate of perforation. The Support Catheter was discontinued prior to commencement of the Pivotal Trial, and the perforation rate in the Pivotal Trial was less than 1%.

The long-term tolerance to wearing the Essure Micro-inserts was found to be “good” to “excellent” in 99% of women who have been followed-up for 1-3 years.

The observed one-year effectiveness rate of 99.5% (98.1%-100%) and the two-year effectiveness rate of 99.4% are comparable to other methods of sterilization currently available.

D. Pivotal Trial of Safety and Effectiveness

The Pivotal Trial of the Essure System was designed as a multi-center, non-randomized, single-arm, international study of women seeking permanent contraception. The study was conducted in the U.S., Europe, and Australia. The targeted study population was 400 women in whom bilateral Micro-insert placement was achieved.

The primary endpoints for this study were:

- ?? Prevention of pregnancy;
- ?? Safety of the Micro-insert placement procedure; and
- ?? Safety of the Micro-insert wearing.

The secondary endpoints for this study were as follows:

- ?? Participant satisfaction with the Micro-insert placement procedure;
- ?? Participant satisfaction with Micro-insert wearing;
- ?? Bilateral Micro-insert placement rate; and
- ?? Development of a profile for an appropriate candidate for the Essure procedure.

Study participants were women who were seeking permanent contraception. The study did not include a prospective control group, but instead used findings from the CREST study as a qualitative benchmark.

The study had two phases: 1) the “Post-Device (Micro-insert) placement” (PDP) phase, and 2) the “Post-Alternative Contraception” (PAC) phase. The “Post-Device placement” phase was the time period between Micro-insert placement and the 3-month visit, during which women were instructed to rely on alternative contraception. At the 3-month visit, a hysterosalpingogram (HSG) was conducted to evaluate Micro-insert location and occlusion. Assuming both were satisfactory, women were instructed to discontinue alternative contraception, thus entering the “Post-Alternative Contraception” phase of the study, during which they relied on Essure solely for contraception. If the HSG was not satisfactory, then, depending on the circumstances, women were instructed to either seek alternative contraception or remain in the “Post-Device placement” phase until a second HSG or Micro-insert placement procedure was performed.

The visits in the study are described as follows:

Micro-insert Placement

Women underwent the Micro-insert placement with typically either local anesthesia alone or with IV sedation. Following the placement procedure women completed a questionnaire on pain assessment and satisfaction.

One-Week

During the first week after the procedure, women were asked to complete a series of questionnaires to evaluate recovery and satisfaction. In addition, there was a phone visit at the one-week time point that served to remind women of the need for alternative contraception, and to assess any adverse events.

3-Month Post-Device Placement (PDP) Visit

Women were then seen at the 3-month post-device placement follow-up visit.

This visit included:

- ?? Pelvic exam
- ?? Pregnancy test
- Verification of partner fertility and coital activity
- Questions on satisfaction, adverse events, concomitant medications, etc.
- HSG to evaluate Micro-insert location and tubal occlusion

Once the HSG was evaluated, if the Micro-inserts were in satisfactory location and the tubes were occluded, women were advised to rely on Essure for contraception. If the Micro-inserts were in satisfactory location, but the tubes were not occluded, then women were advised to continue alternative contraception and return for a repeat HSG 3 months later. If occlusion was demonstrated by the second HSG, then women were

instructed to discontinue alternative contraception. If the tubes remained patent, then women were counseled about other contraception and advised not to rely on the Essure Micro-inserts.

Post-Alternative Contraception (PAC) Phase

Phone follow-up visits were scheduled for 3, 6 and 18 months of reliance on the Micro-inserts for contraception. The phone visits include questions on:

- ?? Verification of coital activity, sole reliance on Essure, and partner fertility
- ?? Satisfaction/Comfort
- ?? Plans for intrauterine procedures or extirpative surgery of reproductive organs
- ?? Adverse events or unusual symptoms

Office visits were scheduled annually at years 1-5 (with the first year to be completed pre-approval and the remaining 4 years to be completed under post-market surveillance). These visits included:

- ?? Pelvic exam,
- ?? Pregnancy test,
- ?? X-ray verification of Micro-insert retention,
- ?? Verification of coital activity, sole reliance on Essure, and partner fertility,
- ?? Questions regarding comfort and overall satisfaction,
- ?? Questions regarding any plans for intrauterine procedures or extirpative surgery of reproductive organs, and
- ?? Adverse events or unusual symptoms.

Summary of Study Results

Placement Rates

Of the 507 women in whom an Essure System was used, bilateral placement was achieved in 464 (92%), and single Micro-insert placement was achieved in 2 women with a unicornuate uterus (100%). Of the 41 (8%) women with bilateral tubes who did not achieve bilateral placement, 15 (37%) were found to have proximal tubal occlusion (PTO) on follow-up HSG. Eliminating these women from the analysis of placement rates results in an overall bilateral placement rate of 464/494 (94%).

Satisfactory Micro-insert Location/Occlusion Rates

A total of 456 women with bilateral placement completed the 3-month post-device placement visit and underwent an HSG. Of those 456 women, 437 (96%) were noted on HSG to have Micro-inserts in satisfactory location. Of those 437 women, 421 (96%) were also noted to have bilateral tubal occlusion. Nine of the women with Micro-inserts in unsatisfactory location (expulsion due to improperly placed Micro-insert) returned for a second placement procedure to replace the expelled Micro-insert. All achieved bilateral placement and were found on follow-up HSG to have bilateral occlusion and Micro-inserts in satisfactory location. All of the 16 women who had tubal patency at the initial HSG chose to undergo a second HSG 3 months later, and all were found to have bilateral occlusion on the second HSG. Therefore, of the 456 women with bilateral placement completing the 3-month visit, 446 (98%) were ultimately found to have Micro-inserts in satisfactory location and bilateral occlusion.

Reliance Rates

As stated above, 446/456 women with bilateral placement were able to rely on Essure for contraception. In addition, 3 women with bilateral

placement who did not have an HSG chose to begin relying on Essure. Also, there were four women with unilateral placement and either confirmed contralateral PTO (2) or a unicornuate uterus (2) who were able to rely on Essure for contraception. Among the 507 women in whom an Essure System was used, 453 (89%) were ultimately able to rely on Essure for contraception.

Adverse Event Rate

Adverse events on the day of the placement procedure were reported in 17 (3%) women. All events were resolved prior to the woman being discharged, except for one woman who required overnight observation following an adverse reaction to pain medication. Day of procedure events included the following, all of which occurred in <1% of cases: vomiting, vasovagal response, hypervolemia, band detachment, perforation, excessive vaginal bleeding, and “other” (skin itching, bloating, loss of appetite, and reaction to saline used for distension).

Adverse events that *initially* prevented the woman from relying on Essure occurred in 21 (4.5%) women. These were primarily Micro-insert expulsions following original Micro-insert placement that was out-of-specification. Nine of the women who experienced an expulsion chose to undergo a second placement procedure, and all were successful. Therefore, adverse events that *ultimately* prevented reliance occurred in only 12 (2.6%) women. The most frequently reported adverse events reported in the first year that did not prevent the woman from relying on Essure, but were rated by the Investigator as at least “possibly” related to Essure were back pain (8.4%), and abdominal pain/cramps (3.4%). All other events occurred in less than 3% of women.

Patient Satisfaction/Comfort

Women in the study consistently rated their overall satisfaction and comfort in wearing the Micro-inserts as very high. At all study visits after the One-Week phone visit, 99% of women rated their comfort with wearing Essure as “good” to “excellent”. At all study visits, at least 98% of women rated their overall satisfaction as some what to very satisfied (this included women who were not able to rely on Essure).

Pregnancy Prevention

There have been no pregnancies in any of the 452 women who are currently relying on Essure for contraception in the Pivotal trial. 408 women in the Pivotal Trial have been followed for at least one-year after relying on Essure for contraception, with all others ranging from 7-11 months of effectiveness. Combined with data from the Phase II study⁴, this equates with over 620 women-years of first year effectiveness evaluation (and over 270 woman-years of second year evaluation) and the current estimate of the one-year effectiveness rate based on these combined data is 99.8%.

⁴ One woman in the Phase II study who received a prior device design that was discontinued in 1998 (the Beta design of the STOP device) became pregnant after nearly two years of reliance. That pregnancy is not included in the effectiveness rate calculations, since that device design is not the subject of this PMA.

IX. CONCLUSIONS DRAWN FROM STUDIES

In vitro assays, acute and sub-chronic animal studies revealed no evidence of local or systemic toxicity, or undesirable tissue response. Results of *in-vitro* cytotoxicity testing were negative. Results of a 12-week *in-vivo* mutagenicity study in female p53+/- cll double transgenic mice resulted in no adverse toxicological effects and no increase in gene mutations at the site of implantation. Results of a 26 week toxicity study in rabbits showed no adverse local device effects or systemic toxicity. An *in-vitro* study of the safety and compatibility of Essure with MRI showed that Essure was safe at 1.5 tesla, though image artifact in local tissues was likely.

The human clinical data provide a reasonable assurance based on valid scientific evidence that the Essure System has been shown to be safe overwhelmingly acceptable to women, and effective, with a one-year effectiveness rate of 99.8% and a two years effectiveness rate from the Phase II study of 99.4%.

X. RISK/BENEFIT ANALYSIS

A. Risks

The most significant risk with the Essure method noted in the Pivotal Trial was the inability to rely on the Micro-inserts for contraception, due either to inability to place the Micro-inserts initially (8%), or misplacement of the Micro-inserts resulting in perforation, proximal placement leading to expulsion, or other unsatisfactory Micro-insert location (initially 4.5%, ultimately 2.6%). The following should be considered, however, when evaluating this risk:

?? The inability to rely on Essure for contraception is mostly due to the inability to place the Micro-inserts during the initial placement

procedure. Such women have only undergone the risk of the hysteroscopic placement procedure, and are not at risk for any complication related to device wearing. The risks associated with the placement procedure are infrequent and insignificant, especially as compared to the serious complications and deaths that can occur with current tubal sterilization procedures.

- ?? The most common causes for placement failure were stenotic or previously occluded tubes. These conditions were diagnosed by the failed hysteroscopic tubal cannulation procedure and/or a follow-up HSG. Therefore, while these women would then be contraindicated for Essure, if those with occluded tubes were to have chosen incisional tubal sterilization instead of Essure, they would have unnecessarily undergone more invasive tubal occlusion surgery, with its attendant risks. Although the pre-existing tubal occlusion was not diagnosed pre-operatively, the risks associated with a hysteroscopic procedure are typically less serious than the risks associated with laparoscopy or laparotomy and the general anesthesia that is typically used in such approaches.
- ?? Women who cannot rely on the Micro-inserts for contraception due to misplacement of the Micro-inserts during the initial placement procedure, were primarily composed of those women who experienced a Micro-insert expulsion. All women who experienced a Micro-insert expulsion and chose to undergo a procedure to replace the expelled Micro-insert(s), achieved bilateral placement and were therefore ultimately able to rely on the Essure for contraception. In addition, Micro-insert expulsion itself has not caused any long-term or serious adverse clinical sequelae, and is easily diagnosed. Finally, it should be noted that the Pivotal Trial protocol did not allow removal of misplaced Micro-inserts. The commercial labeling, however, allows removal of Micro-inserts that have 18 or more coils trailing into the

uterine cavity. This should significantly reduce the risk of expulsions in the commercial setting.

- ?? The women who could not rely on the device due to perforation comprise the smallest percentage of women who cannot rely on Essure due to an adverse event (0.9% of the study population). These women did not suffer any long-term or serious adverse clinical sequelae, other than having to undergo incisional tubal sterilization to complete their sterilization.
- ?? The women who were unable to have successful bilateral placement of the Micro-inserts were immediately informed that the procedure was not a success. Thus, the women for whom the Essure System was not successful, were informed of the fact, and were never at risk of pregnancy.
- ?? In comparing the placement rates with the Essure method to incisional tubal ligation, it should be noted that women who undergo incisional tubal ligation are pre-selected, in most medical practices, to eliminate those women who might not be successful candidates or in whom the risk of intra-operative complications is increased (obesity, prior abdominal/pelvic surgery, etc.). Essure, in fact, had very high placement success in these very women.

None of the adverse events that occurred in the Pivotal Trial resulted in unintended major surgery, re-hospitalization, or death, as occurs with incisional tubal sterilization, although rarely.

B. Benefits

The main benefit of the Essure method is that it provides permanent birth control without invasive surgery or general anesthesia, and their attendant risks. The ability to perform tubal occlusion without invading the

peritoneal cavity or general anesthesia has resulted in the following benefits:

1. The majority of women who work missed less than one day of work following the day of the procedure.
2. The majority of women returned to normal activities within one day or less.
3. The vast majority of women rated their satisfaction with speed of recovery as “very satisfied”.
4. The vast majority of women rated their comfort with wearing the Micro-inserts at one-week as “good” to “excellent”.
5. The complications associated with the placement procedure were infrequent and insignificant.

In addition to the above benefits, none of the women in the Pivotal Trial became pregnant while relying on Essure for contraception. It is not surprising, therefore, that the vast majority of women rated their overall satisfaction with this method as “very satisfied”. Finally, it should be noted that women who would otherwise have a relative contraindication for transabdominal tubal sterilization (due to obesity or prior abdominal/pelvic surgery), had placement rates in the Pivotal Trial as high as women without these conditions. In addition, women who are otherwise poor candidates for incisional surgery, such as the women in the Pivotal Trial who were taking warfarin (Coumadin) or had been diagnosed with multiple sclerosis, have no contraindications for Essure placement. Therefore, the Essure System can be used in women who would otherwise not be candidates for invasive sterilization.

Finally, Essure does not contain drugs or hormones.

X. PANEL RECOMMENDATIONS

To be completed by FDA.

XI. CDRH DECISION

To be completed by FDA.

XII. APPROVAL SPECIFICATIONS

To be completed by FDA.